# Perioperative use of phenylephrine
## *Could it be more harmful than helpful ?*

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# Disclosures

| | |
|---|---|
| **Research Support/P.I.** | **Amomed Pharma, Masimo Inc** |
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| **Honoraria** | **Orion Pharma, Masimo Inc, Edwards Lifesciences, Amomed Pharma, LFB** |
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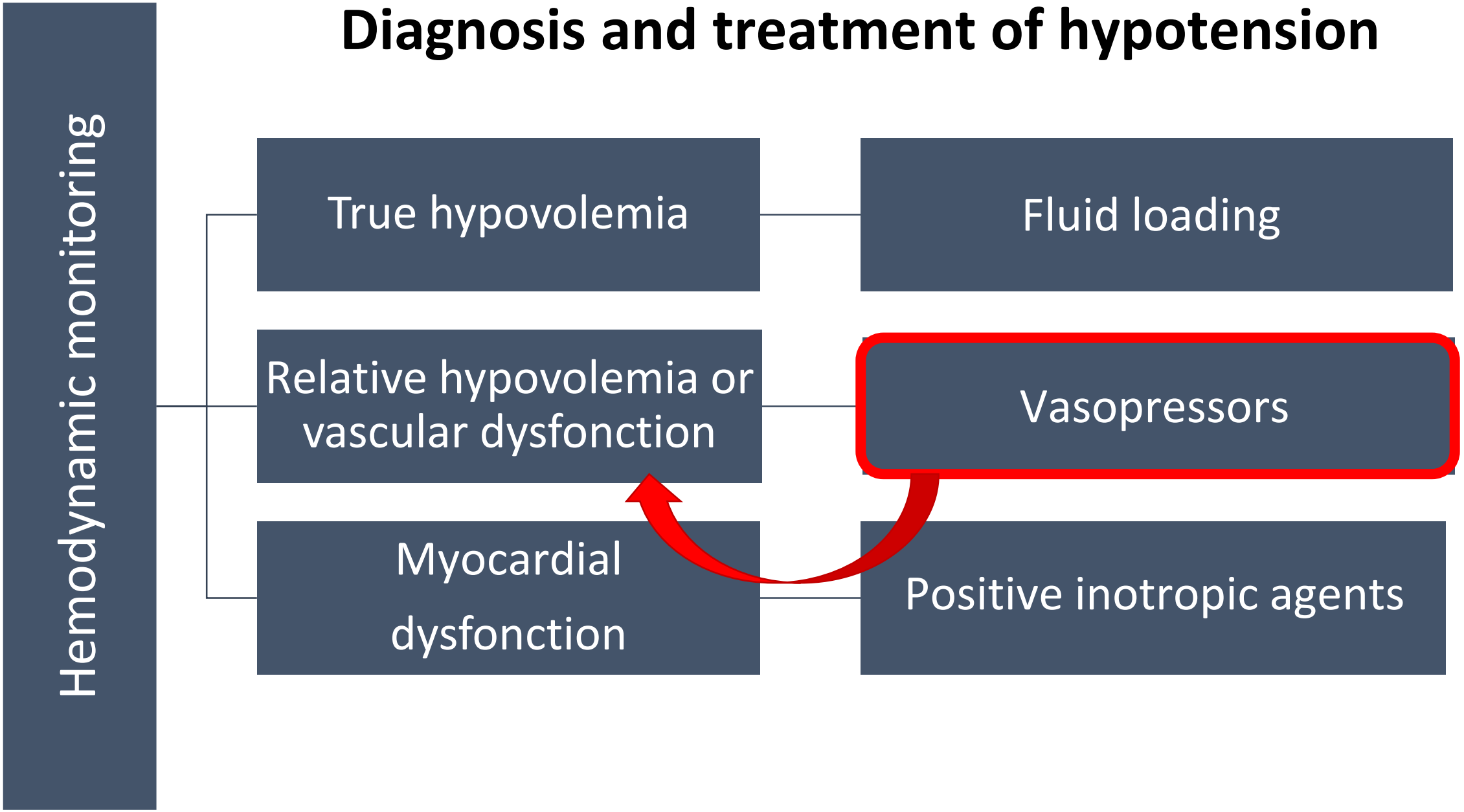
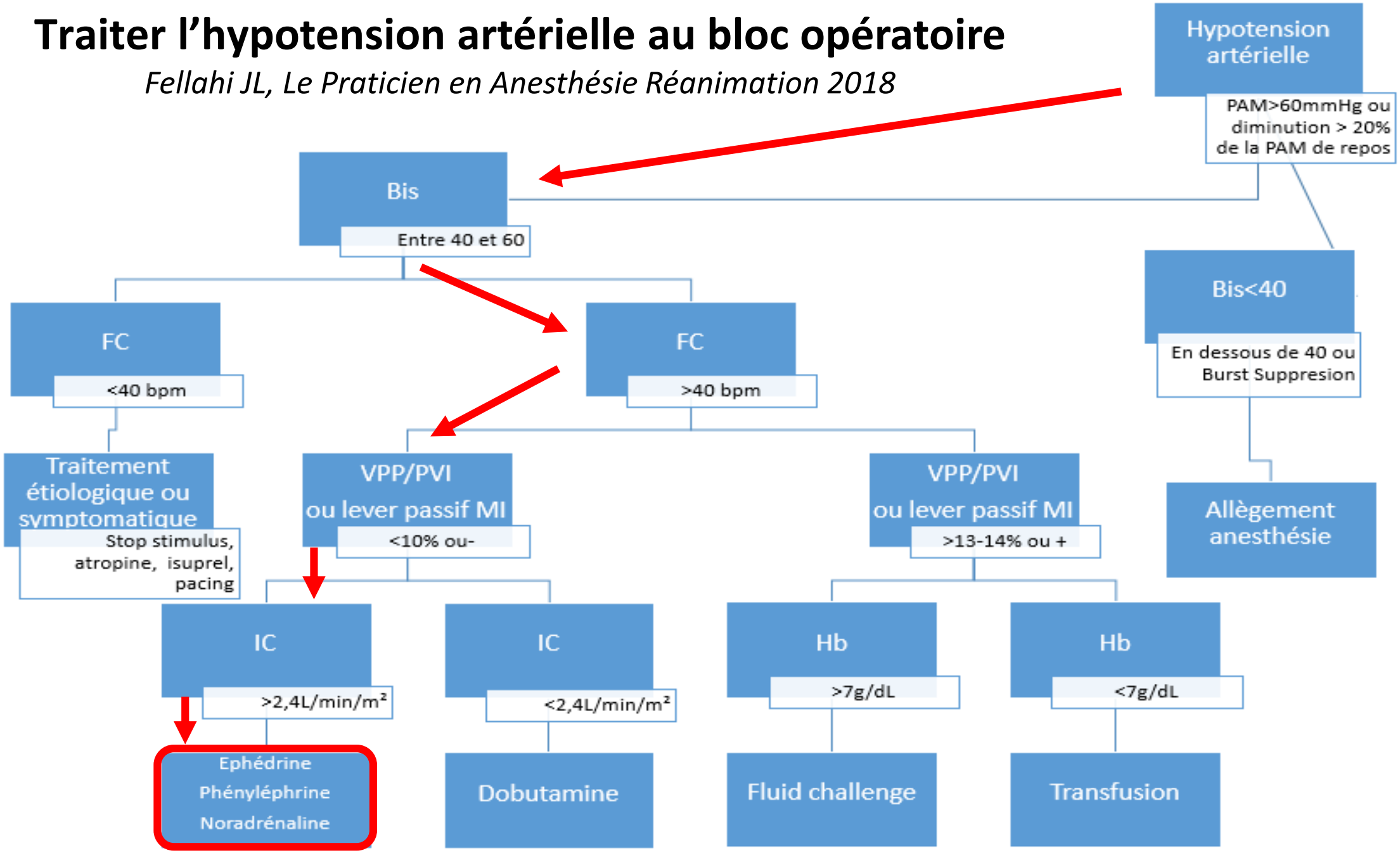
# Diagnosis and treatment of hypotension



# Traiter l'hypotension artérielle au bloc opératoire

*Fellahi JL, Le Praticien en Anesthésie Réanimation 2018*



# Vasoactive Drugs in Circulatory Shock

β effect

Isoproterenol

Dopexamine

α and β effects

Dobutamine

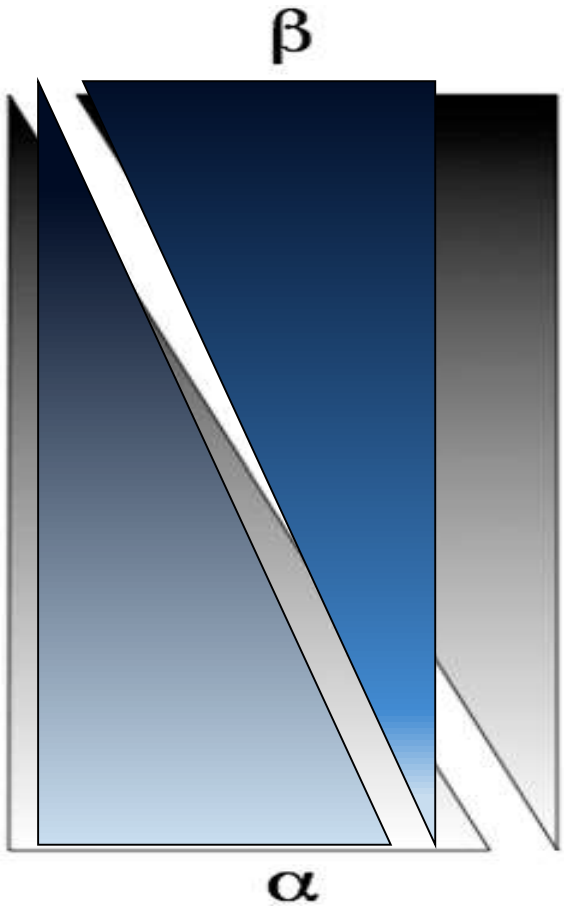
Dopamine

Epinephrine

Norepinephrine

α effect

Phenylephrine




*Hellenberg et al. Am J Respir Crit Care Med 2011*

# Three main therapeutic options …

1

**Ephedrine**


2

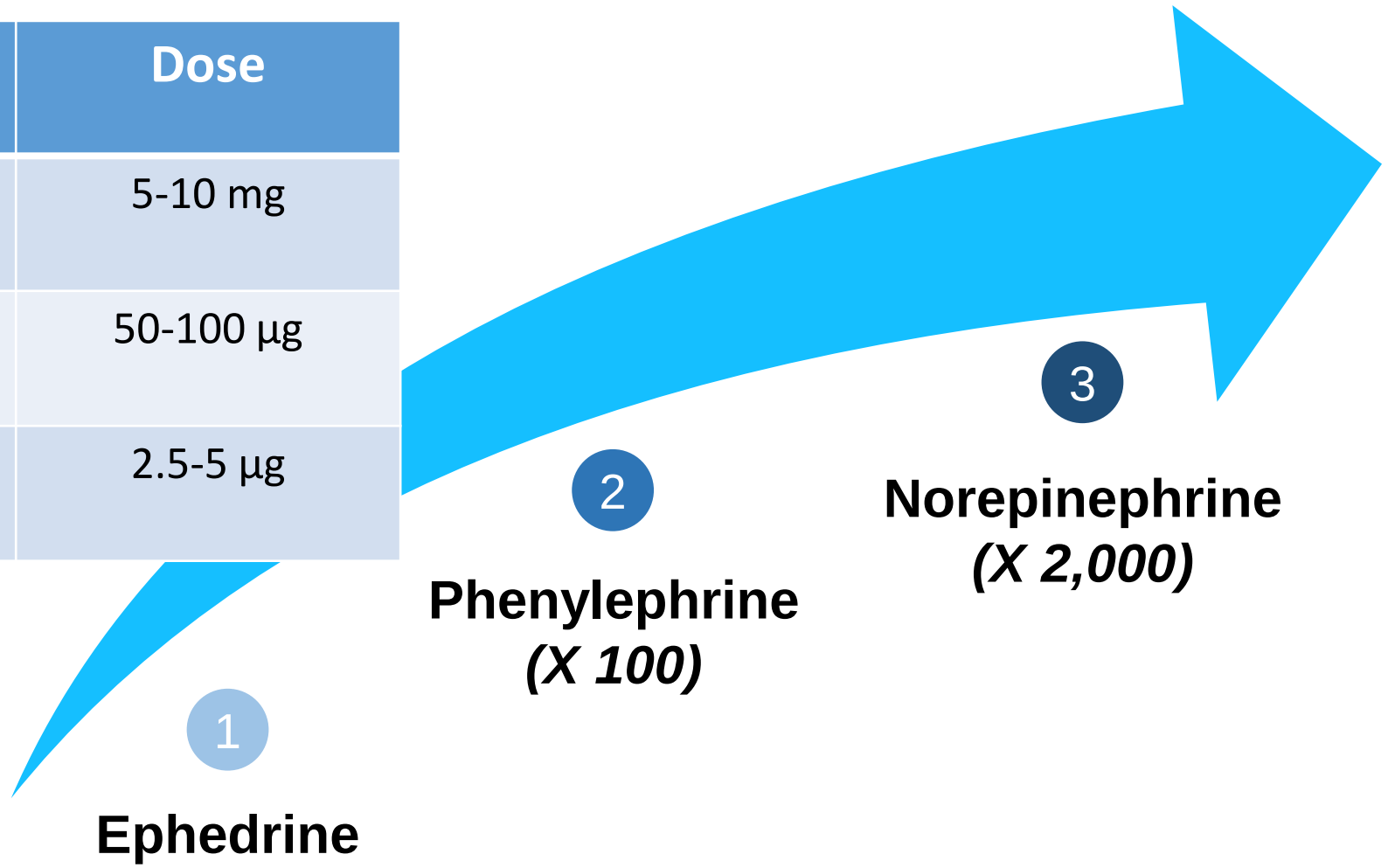
**Phenylephrine**


3

**Norepinephrine**

# Pharmacological properties

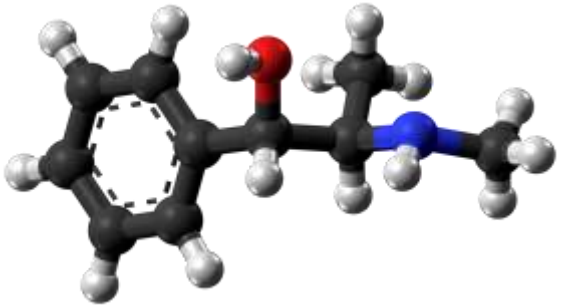
| Drug | Dose |
|---|---|
| Ephedrine | 5-10 mg |
| Phenylephrine | 50-100 µg |
| Norepinephrine | 2.5-5 µg |



# Ephedrine

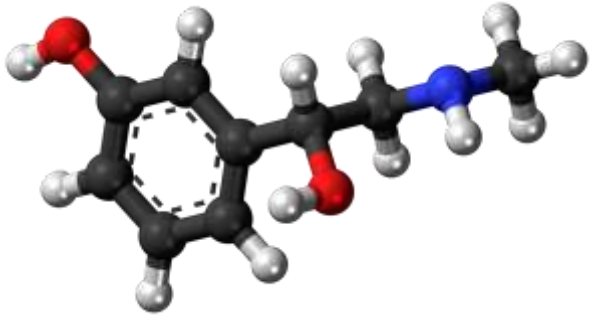
| Myocardium | | | Vessels | | |
|---|---|---|---|---|---|
| β1 | β2 | α1 | α1 | β2 | D1 |
| + | | + | + | + | |

α indirect effect (endogenous norepinephrine)



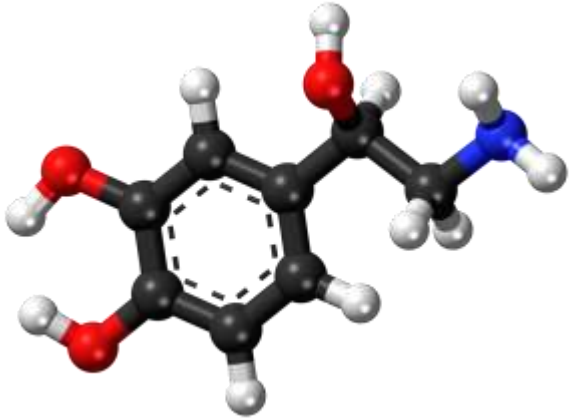
# Phenylephrine

| Myocardium | | | Vessels | | |
|---|---|---|---|---|---|
| β1 | β2 | α1 | α1 | β2 | D1 |
| | | + | + | | |



# Norepinephrine

| Myocardium | | | Vessels | | |
|---|---|---|---|---|---|
| β1 | β2 | α1 | α1 | β2 | D1 |
| + | | + | + | + | |



Ces différences ont-elles un impact clinique pour la correction de l'hypotension artérielle au bloc opératoire ou peut-on s'en tenir à de simples considérations pratiques ?

***Il existe des seringues d'éphédrine ou de phényléphrine préremplies et prêtes à l'emploi ce qui n'est pas le cas de la noradrénaline***

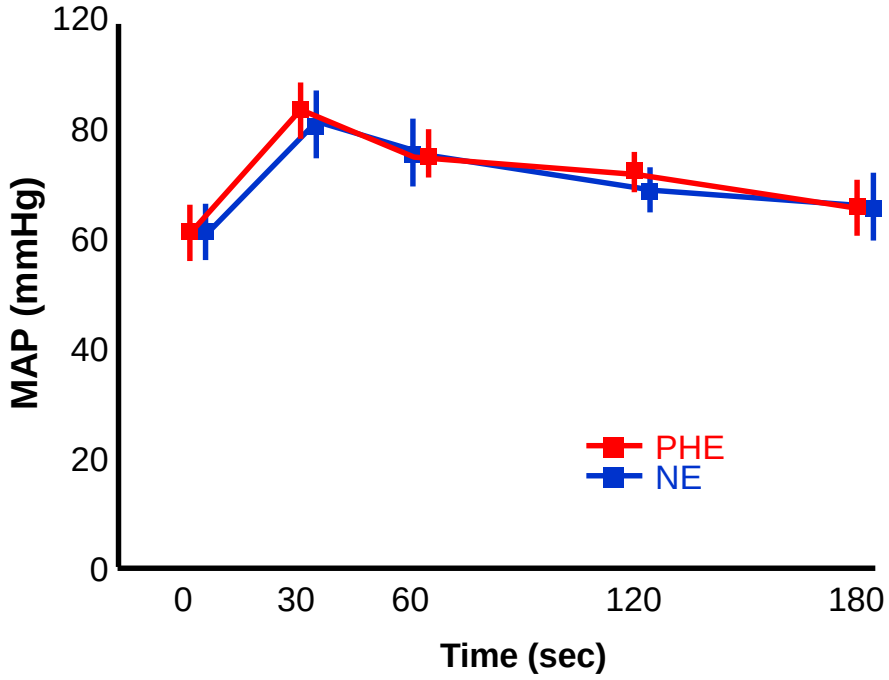
**Erreur médicamenteuse**

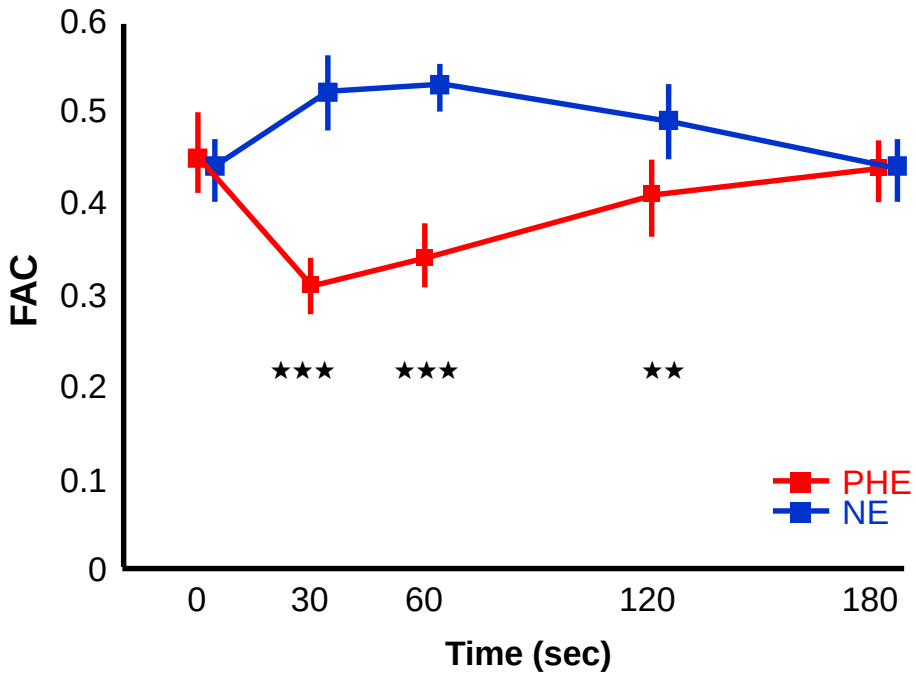
# The Effect of Phenylephrine Bolus Administration on Left Ventricular Function During Isoflurane-Induced Hypotension

16 patients without cardiac disease, isoflurane-related hypotension

Phenylephrine : decrease in LV performance

Norepinephrine : Increase in LV performance



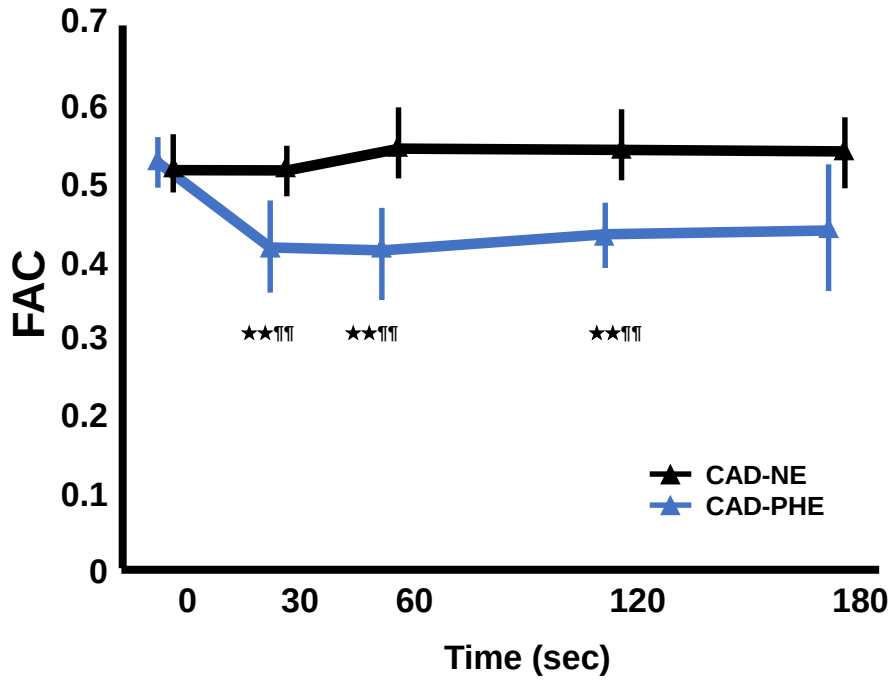



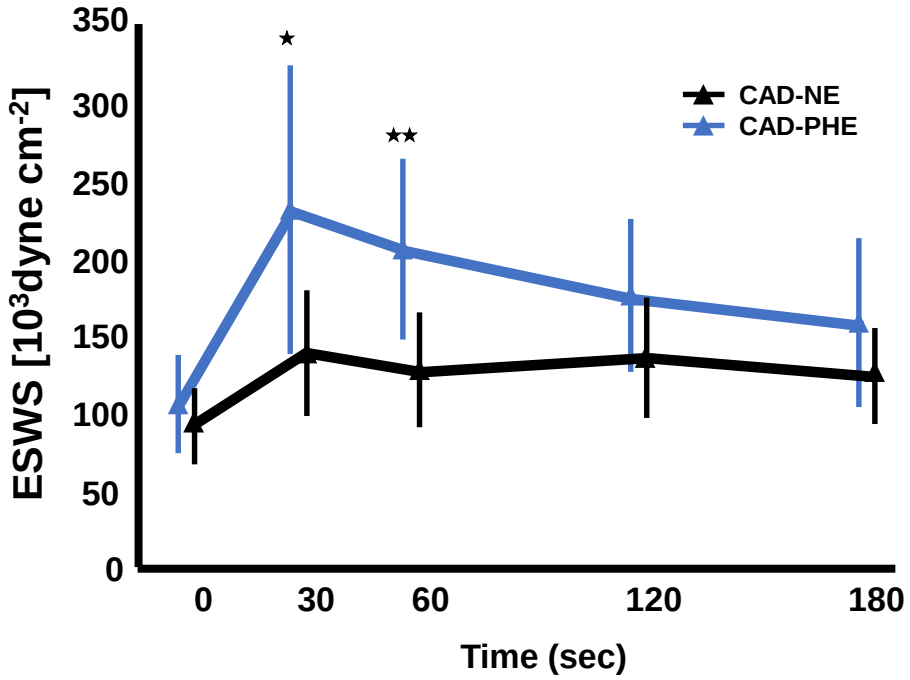

*Goertz et al., Anesth Analg 1993*

**Anesthesiology 1993;78:834-41**


# Effect of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease and patients with valvular aortic stenosis

*Goertz AW,M.D., Lindner KH,M.D., Seefelder C,M.D., Schirmer U,M.D., Beyer M, M.D., Georgieff M, M.D.*



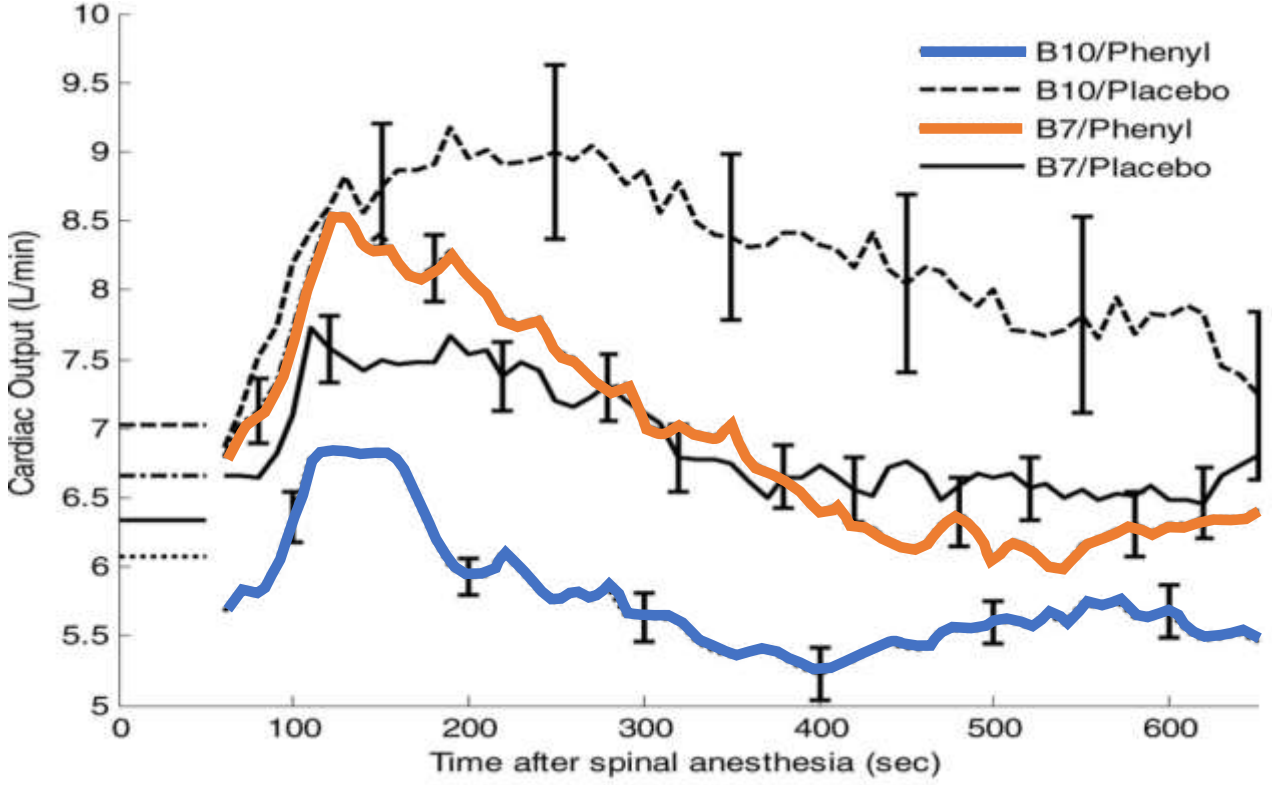
Anesthesiology 2008; 109:856–63

# Continuous Invasive Blood Pressure and Cardiac Output Monitoring during Cesarean Delivery

*A Randomized, Double-blind Comparison of Low-dose versus High-dose Spinal Anesthesia with Intravenous Phenylephrine or Placebo Infusion*

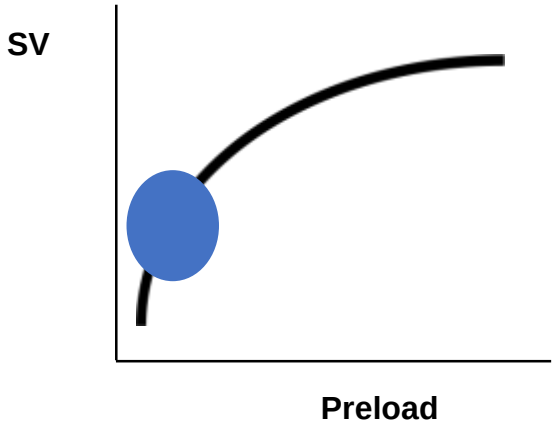
Eldrid Langesæter, M.D.,* Leiv Arne Rosseland, M.D., Ph.D.,* Audun Stubhaug, M.D., Ph.D.†

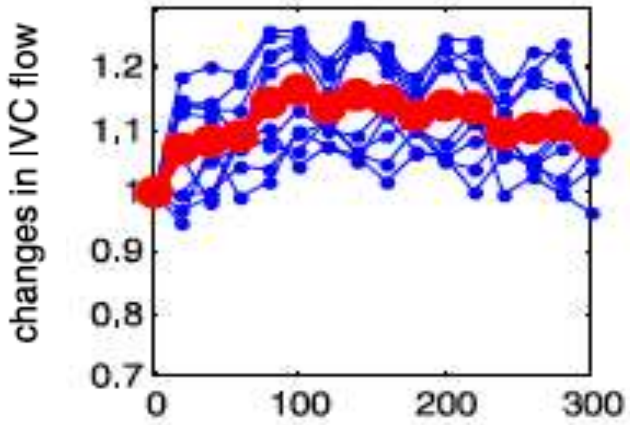
- N=80 healthy pregnant women at term - elective cesarean delivery
- Isobaric bupivacaine 10 mg *vs.* 7 mg
- Fluid loading with 750 ml 0.9% saline
- LiDCO plus

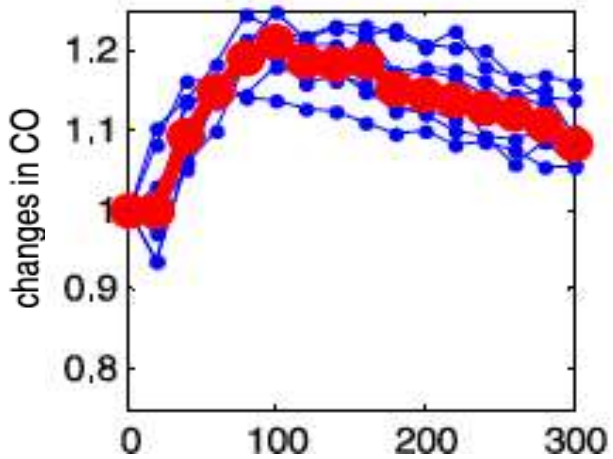


# Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship

8 pigs, acute blood removal 21 ml/kg, phenylephrine use
Animals were preload dependent or independent



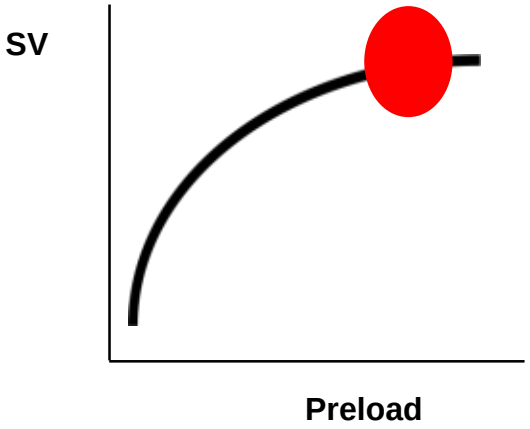



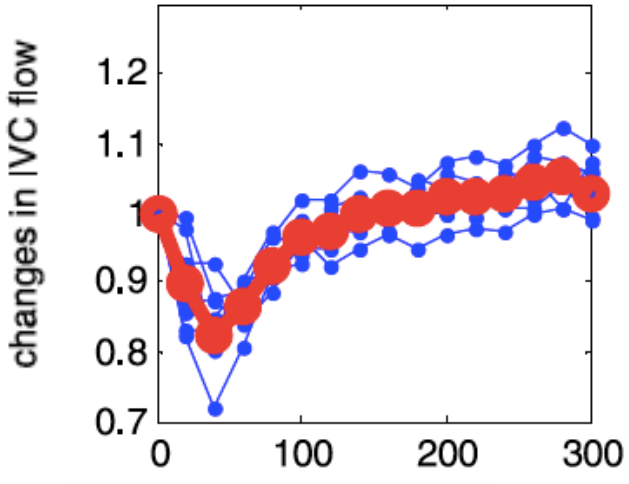

**Preload dependence**
**Venous return and cardiac output were increased**

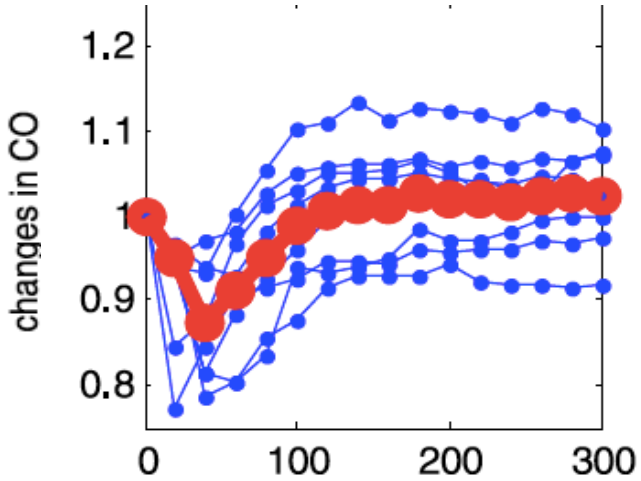
*Canesson et al., J Appl Physiol 2012*

# Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship

8 pigs, acute blood removal 21 ml/kg, phenylephrine use
Animals were preload dependent or independent




**Preload independence → Venous return and cardiac output decreased**

*Canesson et al. J Appl Physiol 2012*

# Preload dependency determines the effects of phenylephrine on cardiac output in anaesthetised patients

*Rebet O, Andremont O, Gerard JL, Fellahi JL, Hanouz JL, Fischer MO*

Eur J Anaesthesiol 2016; 33: 638-644.

50 to 150 µg bolus phenylephrine-induced changes in haemodynamic parameters

| Variable (Δ%) | Preload-dependent N = 27 (PPV ≥ 13%) | Preload-independent N = 23 (PPV < 13%) | *P* value |
|---|---|---|---|
| Heart rate | -8 (8) | -9 (10) | 0.863 |
| Mean arterial pressure | 38 (18) | 33 (15) | 0.282 |
| Systemic vascular resistance | 45 (29) | 70 (38) | 0.013 |
| Cardiac index | -3 (17) | -20 (12) | <0.001 |
| Stroke volume | 5 (13) | -12 (12) | <0.001 |
| Pulse pressure variation | -20 (22) | 4 (40) | 0.01 |
| Flow time corrected | 5.0 (-0.5;7.5) | -3.3 (-9.6;-0.6) | <0.001 |

# Preload dependency determines the effects of phenylephrine on cardiac output in anaesthetised patients

*A prospective observational study*

Olivier Rebet, Olivier Andremont, Jean-Louis Gérard, Jean-Luc Fellahi, Jean-Luc Hanouz and Marc-Olivier Fischer

## Clinical implications

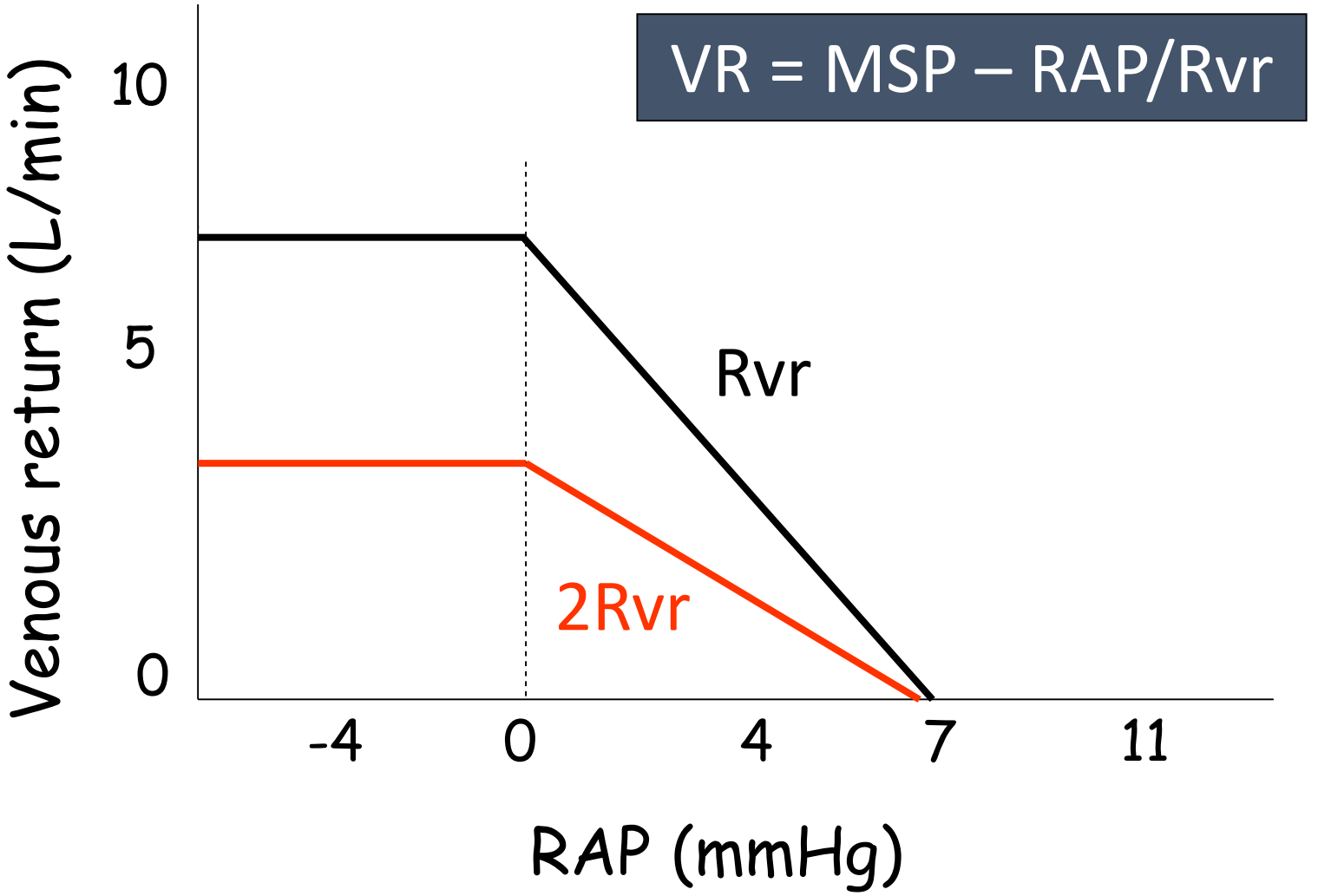
The present study showed a critical phenylephrine-induced decrease in CI in preload-independent patients **which could impair regional oxygen delivery**. In contrast, phenylephrine did not decrease CO in preload-dependent patients. Altogether, these data suggest that **anaesthesiologists should evaluate preload dependency before phenylephrine administration** because the effect on CI is strikingly different.

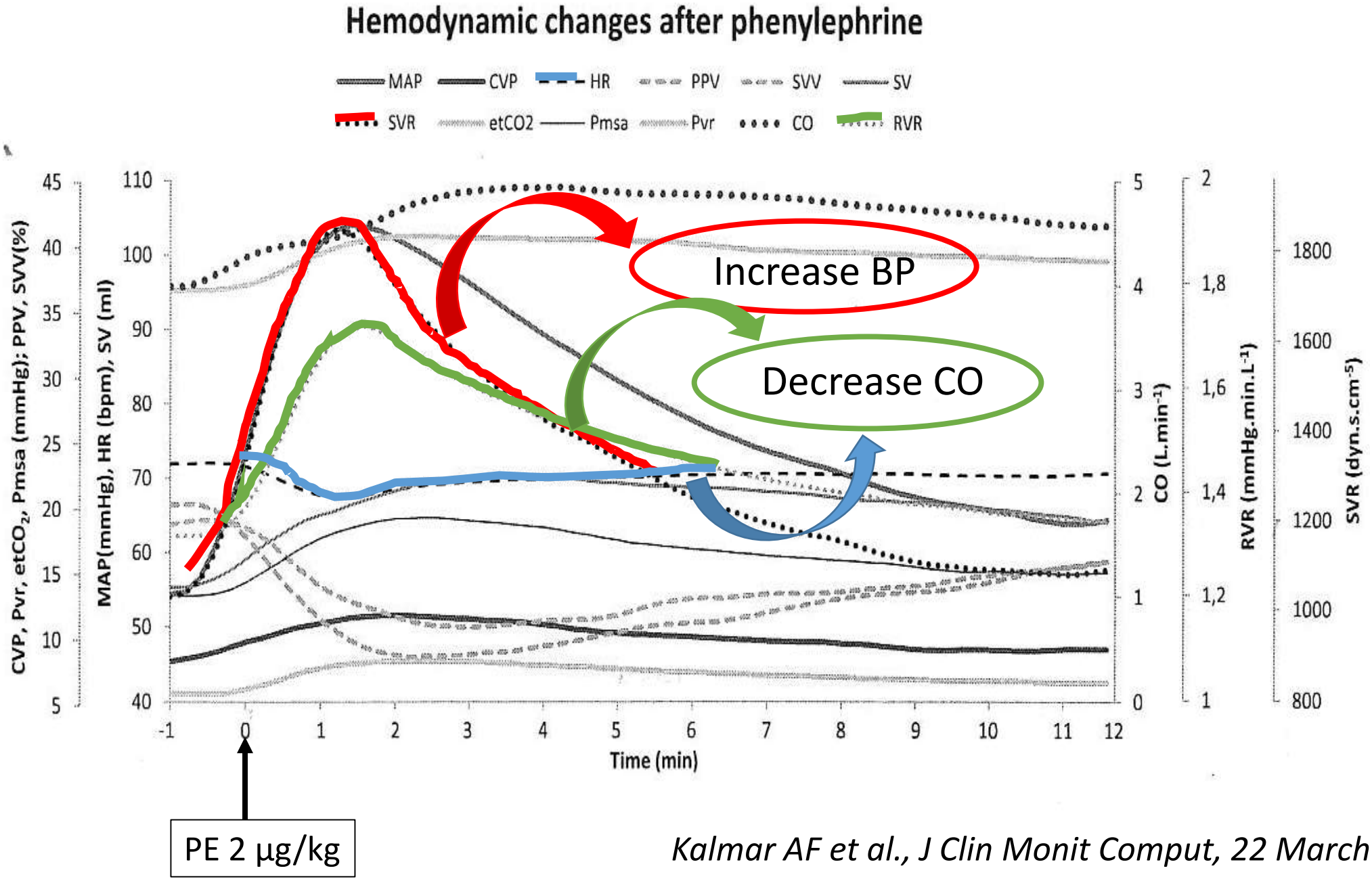
***Eur J Anaesthesiol 2016;33:638–644***

# To summarize: several mechanisms can explain cardiac output decrease with phenylephrine

- An increase in LV afterload induced by a strong arterial vasoconstriction (poor LVEF) *(Goertz 1993)*
- A decrease in heart rate by nearly 10% related to the increase in blood pressure
- A decrease in systemic venous return related to the increase in Rvr (in preload-independent patients) *(Cannesson 2012, Rebet 2016)*

# Venous return curves






*Kalmar AF et al., J Clin Monit Comput, 22 March 2018*

# 29 ASA I-III patients without cardiac disease ; GA-induced hypotension

Treatment with phenylephrine (100-200 µg) or ephedrine (5-20 mg)

+30 (9) mmHg

**MAP**

+24 (13) mmHg

-1.7 (1.0) L/min

**CO**

+0.5 (1.7) L/min

-4.9 (2.8) %

**$rSO_2$**

-0.4 (2.3) %

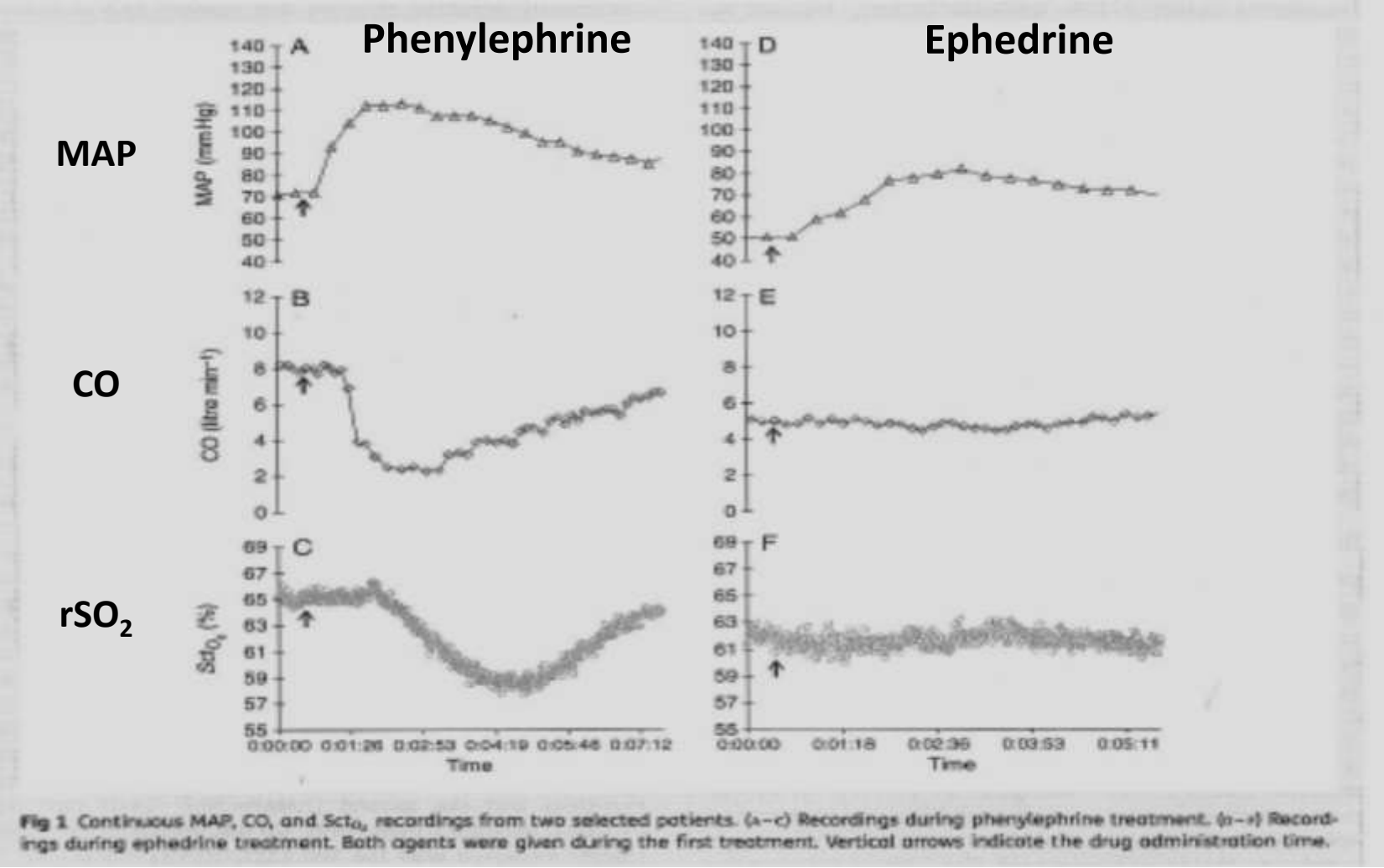



Fig 1 Continuous MAP, CO, and Sct$O_2$ recordings from two selected patients. (a–c) Recordings during phenylephrine treatment. (d–f) Recordings during ephedrine treatment. Both agents were given during the first treatment. Vertical arrows indicate the drug administration time.

*Meng et al., Br J Anaesth 2011;107:209-217.*

ANESTHESIOLOGY

# Cerebral Macro- and Microcirculation during Ephedrine *versus* Phenylephrine Treatment in Anesthetized Brain Tumor Patients: A Randomized Clinical Trial Using Magnetic Resonance Imaging

Klaus U. Koch, M.D., Irene K. Mikkelsen, M.Sc., Ph.D., Ulrick S. Espelund, M.D., Ph.D., Hugo Angleys, M.Sc., Ph.D., Anna Tietze, M.D., Ph.D., Gorm V. Oettingen, M.D., Ph.D., Niels Juul, M.D., Leif Østergaard, M.D., M.Sc., Ph.D., D.M.Sc., Mads Rasmussen, M.D., Ph.D.

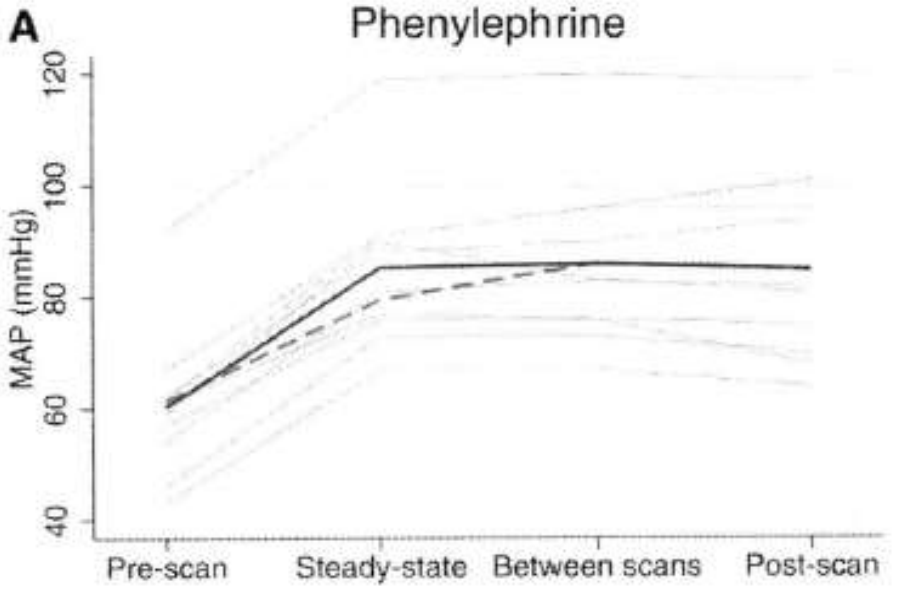
*Anesthesiology 2021; 135:788–803*

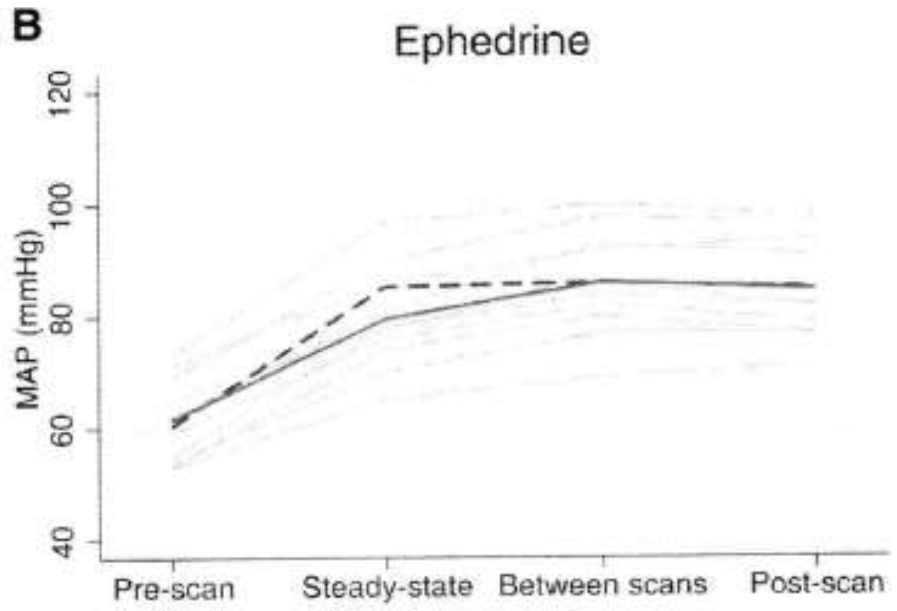
Single-center, double-blind, randomized clinical trial
N = 24 patients

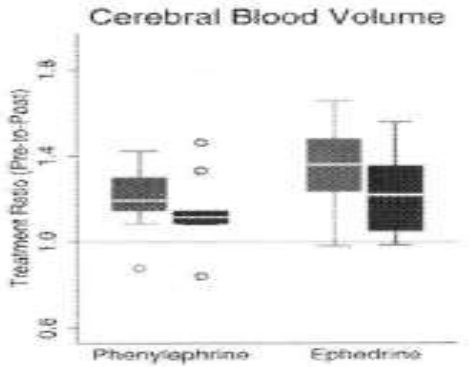
**Primary endpoint**: difference in capillary transit time heterogeneity

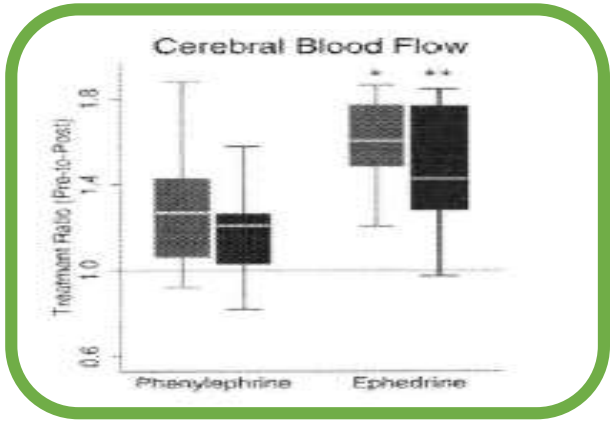
**Secondary endpoints**: changes in cerebral blood flow, brain tissue oxygen tension

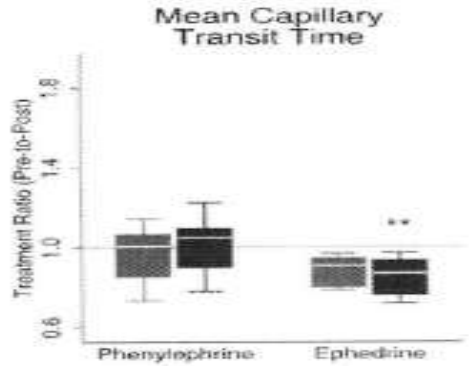
*Ephedrine and phenylephrine titrated to increase MAP above 60 mmHg or by 20%*

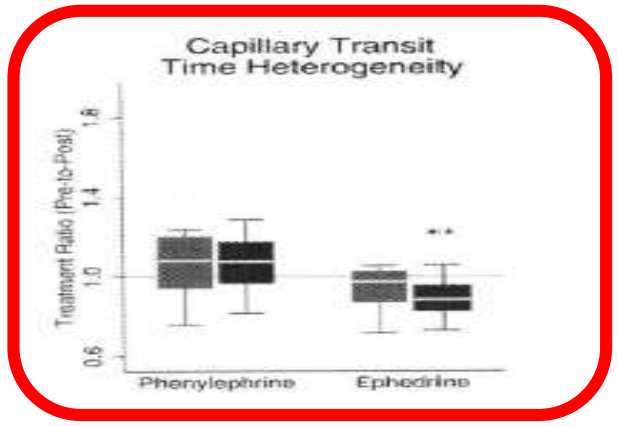

A
Phenylephrine
MAP (mmHg)
120
100
80
60
40
Pre-scan
Steady-state
Between scans
Post-scan

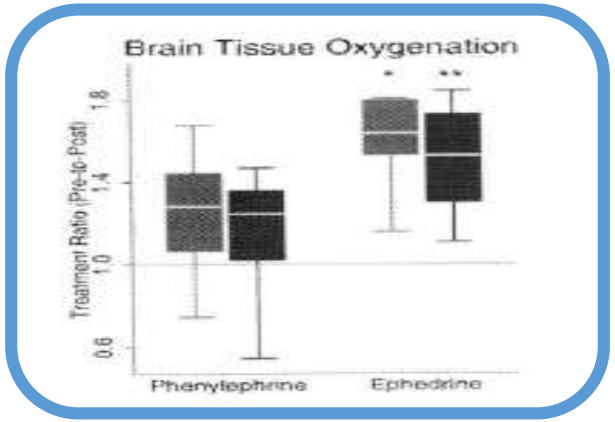

B
Ephedrine
MAP (mmHg)
120
100
80
60
40
Pre-scan
Steady-state
Between scans
Post-scan

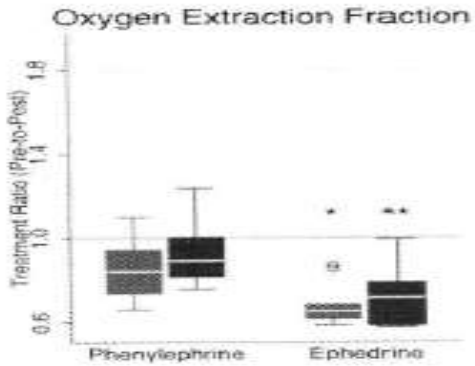

Cerebral Blood Volume
Treatment Ratio (Pre-to-Post)
1.8
1.4
1.0
0.6
Phenylephrine
Ephedrine

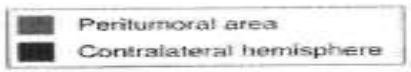

Cerebral Blood Flow
Treatment Ratio (Pre-to-Post)
1.8
1.4
1.0
0.6
*
**
Phenylephrine
Ephedrine


Mean Capillary Transit Time
Treatment Ratio (Pre-to-Post)
1.8
1.4
1.0
0.6
**
Phenylephrine
Ephedrine


Capillary Transit Time Heterogeneity
Treatment Ratio (Pre-to-Post)
1.8
1.4
1.0
0.6
**
Phenylephrine
Ephedrine


Brain Tissue Oxygenation
Treatment Ratio (Pre-to-Post)
1.8
1.4
1.0
0.6
*
**
Phenylephrine
Ephedrine


Oxygen Extraction Fraction
Treatment Ratio (Pre-to-Post)
1.8
1.4
1.0
0.6
*
**
Phenylephrine
Ephedrine


Peritumoral area
Contralateral hemisphere

# Infusion of phenylephrine or norepinephrine in the ICU

**Table 3. Comparison of Norepinephrine with Phenylephrine Infusion to Manage Hypotension in ICU Patients**

| Author | Number of patients | IV administration regimen | Cardiovascular parameters: Heart rate (bpm) | Cardiovascular parameters: Mean arterial pressure (mm Hg) | Cardiovascular parameters: Cardiac index (L/min/m²) | Splanchnic and systemic perfusion: Splanchnic extraction | Splanchnic and systemic perfusion: Hepatic vein $O_2$ saturation gradient | Splanchnic and systemic perfusion: Lactate | Comments |
|---|---|---|---|---|---|---|---|---|---|
| **Cardiac surgery** | | | | | | | | | |
| Nyrgen et al.[57] | NE: 10 | 0.052 ± 0.009 µg/kg/min | 67 ± 9 | NE + PE titrated to reach MAP 30% >baseline | 2.43 ± 0.44 | 43% ± 13%* | 14% ± 11%* | 0.96 ± 0.39 | α = statistically different from baseline (data not shown) |
| | PE: 10 | 0.50 ± 0.22 µg/kg/min | 69 ± 10 | | 2.41 ± 0.35 | 48% ± 16% | 20% ± 12% | 1.09 ± 0.52[α] (mm) | $P = 0.05$ |
| **Septic shock** | | | | | | Blood clearance (ICG) | Creatinine clearance | | |
| Morelli et al.[58] | NE: 15 | 0.82 ± 69 µg/kg/min | 93 ± 18* | NE + PE titrated to MAP of 65–75 mm Hg | 4.9 ± 1.6 | 380 ± 227 | 94.3 ± 93.5* | 1.4 ± 1* | Data: $\bar{x}$ ± SD |
| | PE: 15 | 4.39 ± 5.23 µg/kg/min | 89 ± 18 | | 4.6 ± 1.3 | 330 ± 197 (mL/min/m²) | 81.3 ± 78.4 (mL/min) | 1.7 ± 1 (mm) | NE infusion was replaced with PE infusion for 8 h when data were measured. |
| Morelli et al.[60] | NE: 16 | Infused to maintain MAP at 65–75 mm Hg | 90 ± 18[a] | NE + PE titrated to MAP of 65–75 mm Hg | 4.6 ± 1.5[a] | 280 ± 170[a] | 48 ± 54[a] | 2.6 ± 14[a] | Data: $\bar{x}$ ± SD. Double-blinded infusion study parameters measured after 12 h of infusion. Renal replacement therapy after 12 h. PE = 7 and NE = 2 ($P = 0.133$) |
| | PE: 16 | | 89 ± 19 | | 4.3 ± 1.5 | 260 ± 180 mL/min/m²) | 41 ± 29 (mL/min/1.73 m²) | 2.6 ± 15 (mg/dL) | |
| | | | | | | Splanchnic $O_2$ | Hepatic vein $O_2$ saturation | | |
| Reinelt et al.[59] | NE: 6 | 0.20 (0.07–0.61) µg/kg/min | 107 (79–136) | 72 (68–79) | 4.3 (4.0–7.0) | 1.25 (1.00–5.70)* | 54% (37%–69%)* | 690 (225–930) | Data: median (range) |
| | PE: 6 | 3.20 (1.08–9.62) µg/kg/min | 102 (77–124) | 72 (67–77) | 4.3 (3.9–6.2) | 0.85 (0.80–1.00) (L/min/m²) | 41% (18%–60%) | 248 (188–756) (µmol/min/m²) | |

bpm = beats per minute; ICG = indocyanine green; ICU = intensive care unit; MAP = mean arterial blood pressure; NE = norepinephrine; PE = phenylephrine.
[a]Data derived from graphical representation.
*Statistically different $P < 0.05$.

# La correction de l’hypotension artérielle par la phényléphrine

- S’accompagne au plan macrocirculatoire
  - d’une baisse du débit cardiaque
  - d’une baisse de l’adéquation débit/métabolisme au niveau des organes cibles (cerveau, foie, rein)
- S’accompagne d’une atteinte microcirculatoire au niveau cérébral
- S’accompagne d’une perte de cohérence hémodynamique

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock

Emily Vail, MD; Hayley B. Gershengorn, MD; May Hua, MD, MSc; Allan J. Walkey, MD, MSc; Gordon Rubenfeld, MD, MSc; Hannah Wunsch, MD, MSc

Multicentre retrospective study (26 US hospitals)
27835 septic shock patients between 2008 and 2013
National norepinephrine shortage in 2011 leading to:

- ↘ Norepinephrine: from 77% (IC95%: 76-78) to 56% (IC95%: 52-58)
- ↗ Phenylephrine: from 36% (IC95%: 35-37) to 54% (IC95%: 52-57)

**Increase in hospital mortality ARR: 3.7% (IC95%: 1.5-6.0)**
**from 35.9% to 39.6%**
**aOR = 1.15 (IC95%: 1.01-1.30), *P*=0.03**

THE OPEN MIND

# Should Norepinephrine, Rather than Phenylephrine, Be Considered the Primary Vasopressor in Anesthetic Practice?

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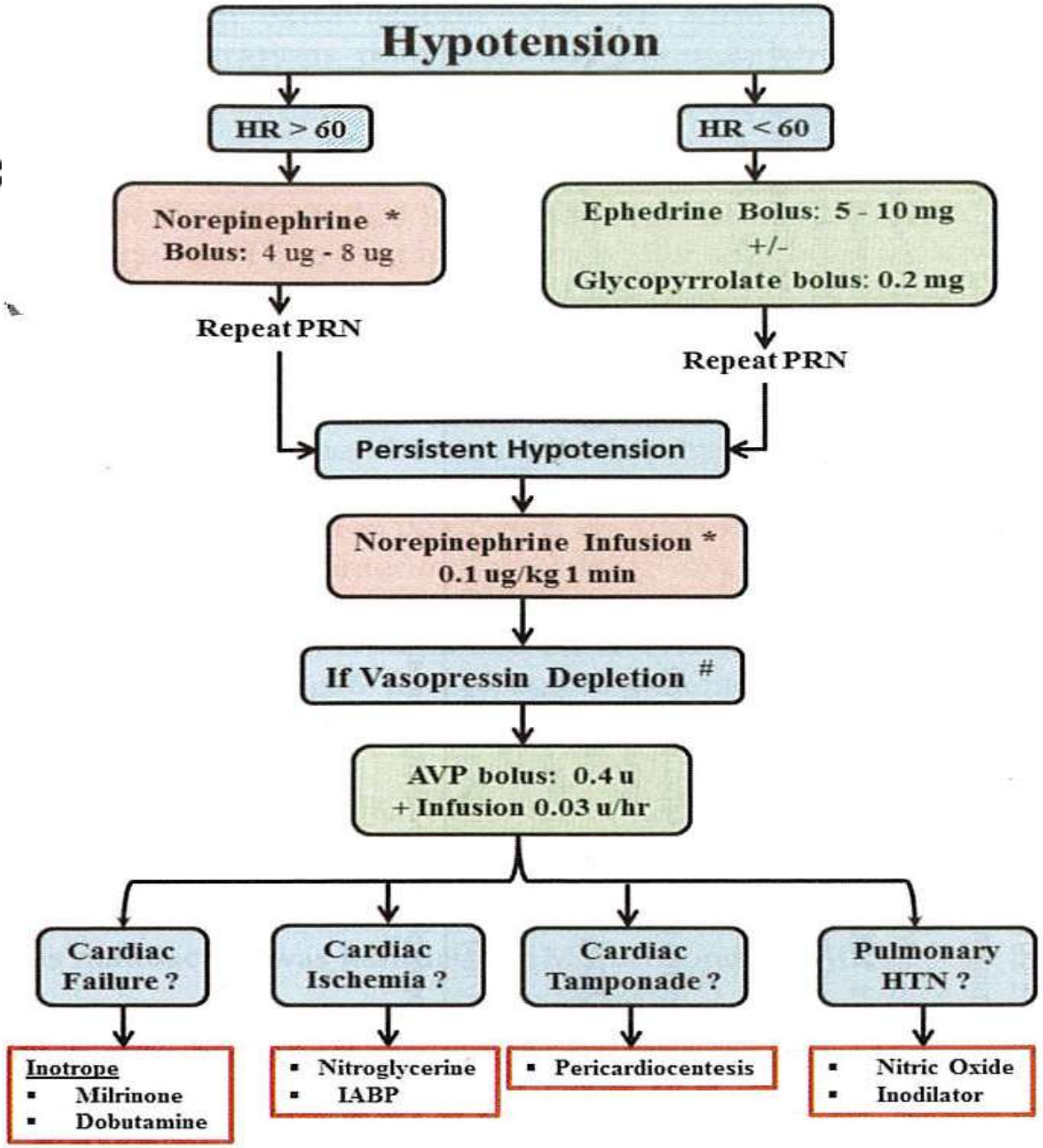
*Anesth Analg 2016;122:1707-1714.*

Phenylephrine:
- Decreases LV performance
- Decreases cardiac output
- Decreases peripheral tissue oxygenation
- Could increase mortality in ICU



# Conclusion

Phenylephrine *(bolus or continuous infusion)* in the OR can be replaced by ephedrine *(bolus)* or « baby norepinephrine » *(bolus or continuous infusion)* with respect of dose equivalence